# Successful Treatment of Metastatic Androgen-Independent Prostate Carcinoma in a Transsexual Patient

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## Abstract

The occurrence of prostate carcinoma in transsexual patients has rarely been reported. These cases present a unique challenge in that such patients are effectively receiving androgen deprivation therapy. By definition, their disease is androgen-independent prostate cancer, and the role of local therapy is undefined. We report on a male-to-female transsexual patient with metastatic prostate cancer treated successfully with combination chemotherapy after previous standard therapy failed.

## Case Report

The 78-year-old patient underwent male-to-female sex reassignment surgery, including bilateral orchiectomy, in 1985. The patient had been receiving estrogenic therapy since 1980. In March 2003, a primary care physician palpated bilateral prostate nodules, and subsequent testing for serum prostate-specific antigen (PSA) revealed a level of 20.6 ng/mL. The concurrent baseline testosterone value was in the castrate range. Prostate biopsy specimens demonstrated adenocarcinoma with a predicted Gleason score of 9 (4+5) from 2 of 6 core biopsy specimens. A staging bone scan reported significant uptake in L4 and L5, which was deemed an arthritic change with no evidence of metastasis in the final impression. No soft tissue imaging was performed. Subsequently, the patient was treated with intensity-modulated radiation therapy (RT) with curative intent.

One month after completing intensity-modulated RT, the serum PSA level was 11.5 ng/mL. A repeat value 6 months later had increased to 89.6 ng/mL; a repeat bone scan revealed extensive osseous metastatic disease. Prostate-specific antigen level reached a maximum of 143 ng/mL, at which time chemotherapy was initiated. The patient was treated with docetaxel 75 mg/m$^2$ every 21 days, with prednisone 5 mg orally twice daily.

After the third dose of docetaxel, follow-up PSA had increased to 177 ng/mL. A repeat bone scan demonstrated significant progression of osseous metastatic disease. The patient received 2 additional cycles of docetaxel before care was transferred to our facility.

At the time of reevaluation, PSA level was 138 ng/mL and testosterone was 46 ng/dL. Imaging of the abdomen and pelvis revealed no soft tissue disease or enlarged lymph nodes. Treatment was initiated with weekly combination chemotherapy as follows: docetaxel (25 mg/m$^2$), carboplatin (area under the curve of 2), and abbreviated estramustine (280 mg orally twice a day on days 1 and 2), administered 3 of 4 weeks. At the patient's request, the patient continued on estrogenic therapy 0.3 mg daily to maintain sex identity as a woman. After 1 month of combination chemotherapy, PSA had declined by > 90% to a value of 16 ng/mL. After 9 doses of weekly chemotherapy (3 cycles), PSA had fallen to 4.1 ng/mL; after the 15th dose, PSA was 0.9 ng/mL. Upon completing chemotherapy, the patient was

treated with maintenance adrenolytic therapy using ketoconazole 200 mg orally twice a day in addition to continued low-dose conjugated estrogen.

The patient remains on endocrine therapy at this time, > 18 months since the last chemotherapy dose. The patient's PSA level remains < 1 ng/mL, and testosterone remains < 50 ng/dL. The most recent staging studies did not show any visceral or nodal disease. Bone scintigraphy demonstrates persistent lesions with abnormalities attributable to healing and without evidence of new lesions.

## Discussion

The case of apparently clinically localized, androgen-independent prostate cancer (AIPC) arising in a male-to-female transsexual is uncommon[1,2] and raises numerous questions regarding the diagnosis and management of prostate cancer in this population. Although the diagnosis of adenocarcinoma is readily performed by pathologists, correct Gleason score assignment is technically difficult in the presence of morphologic changes induced by androgen deprivation and might not convey the same prognostic information as Gleason scores assigned to untreated prostate cancer tissue samples.[3,4]

In this patient, staging studies were suggestive, but not conclusive, of metastatic disease. In such instances, magnetic resonance imaging (MRI) of the spine might help clarify abnormalities detected by bone scan, because MRI is quite sensitive for bone metastases, especially in patients with a PSA level < 20 ng/mL.[5] Additional pelvic imaging with ultrasonography or MRI has historically not reliably detected extraprostatic extension or lymph node metastasis.[6] However, with rapid advancements in imaging technology, patients with high-risk features in clinically localized AIPC are increasingly likely to benefit from further imaging with endorectal MRI or ultrasonography; if extraprostatic disease is detected, a systemic treatment approach would be favored.

Definitive RT, as was given in this case, might have utility in preventing symptomatic local progression; however, the degree of benefit in the setting of localized AIPC is not well described. A descriptive study of men with clinically localized AIPC treated with "curative" RT reported development of metastatic disease in 79% of patients at a median follow-up of 33 months.[7] A second study of 29 men with stage D0 or D1 AIPC reported that 16 of the 29 men presented with urinary obstructive symptoms and were treated with RT. At a median follow-up of 43 months, the local failure rate was 39%, but 80% of patients had metastatic progression of disease.[8] Although the presence of a Gleason pattern 4+5, PSA > 20 ng/mL, and significant palpable abnormality at baseline suggested locally advanced high-grade disease, which is classically treated with combined modality therapy, this approach might not be justified in the asymptomatic individual with AIPC. Rather, the presence of AIPC at diagnosis should prompt referral to medical oncology for consideration of secondary endocrine manipulations or docetaxel-based chemotherapy.

The second major issue illuminated by this case is the use of second-line chemotherapy regimens in AIPC. The patient was treated initially with docetaxel/prednisone therapy, which has recently been declared the standard, based on 2 large randomized clinical trials.[9,10] No significant PSA response was documented despite 5 cycles of treatment; in fact, progressive disease was noted on scintigraphy after 3 cycles. At the time of referral to our practice, the PSA level was 138 ng/mL, representing only a 22% reduction in serum PSA. Contemporary intervention studies in metastatic AIPC have defined a sustained decline in PSA of > 50% as a prognostic factor for progression-free and overall survival.[11] However, before declaring such a patient refractory to docetaxel or taxanes in general, practitioners should consider the activity of alternative docetaxel schedules and combinations. Among other factors, the increasing use of chemotherapy "holidays" in patients with advanced cancer requires that clinicians assess time off treatment before categorizing patients as having experienced progression on docetaxel chemotherapy. Clinical trials intending to evaluate second-line therapy in AIPC must be similarly vigilant in defining taxane-refractory disease.

The overall benefit of every-21-day docetaxel in the registration trials was relatively modest, with a 25% relative reduction in death and a median survival of 20 months. Clearly, optimizing the schedule of administration and combining novel agents with docetaxel might significantly extend its value in the future. Recent randomized trials of docetaxel in metastatic AIPC have included 3-weekly and weekly schedules of docetaxel, with and without oral estramustine.[9,10] The addition of estramustine in this case in addition to having antineoplastic effect by interfering with microtubules might have added efficacy to the therapeutic regimen by maximizing testosterone depletion.[12] Additionally, other cytotoxic drugs, antiangiogenic agents, and novel molecules have been combined with docetaxel in phase II trials, resulting in high rates of PSA response and sustained biochemical remissions. These include programs using docetaxel with or without carboplatin,[13,14] high-dose calcitriol,[15] or low-dose oral thalidomide.[16] In the absence of an available clinical trial or a second-line regimen of proven benefit, using an alternative taxane-based regimen, as was done in this case, is a reasonable option in patients who have experienced progression on standard docetaxel/prednisone.

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